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Eligibility for treatment with omalizumab in Italy and Germany

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Summary
Omalizumab is an add-on therapy for patients with uncontrolled severe allergic asthma. In Europe, patients must fulfil a number of additional criteria to become eligible for omalizumab therapy, creating a challenge for epidemiology studies to quantify the potential patient pool. Thus, and in the absence of robust data, the number of omalizumab-eligible patients has remained unclear.

To assess eligible patient numbers, a chart-audit design approach was employed to measure epidemiology variables based on patient-level data. 770 patient charts were reviewed in designated towns in Germany and Italy, in collaboration with >200 primary care physicians (PCPs) and respiratory specialists (RS). This study sample represents >50% and >70% of local RS in these designated towns of Germany and Italy, respectively.

Of patient charts evaluated, 4 patients were currently receiving omalizumab. A further 31 patients (12 PCP; 19 RS) were evaluated as omalizumab-eligible (i.e. fulfilled all product label criteria) but were not receiving the drug. Extrapolating to a national level, this yields >6500 eligible patients in Germany, and >3200 in Italy. Furthermore, this study sample revealed a significant number of PCPs treating uncontrolled severe asthma patients without referral to RS; these patients are not consistently evaluated for FEV_1, aero-allergen sensitivity, a qualitative understanding of severe exacerbations, and day and night-time symptoms.

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This study suggests that significant numbers of omalizumab-naïve severe allergic asthma patients in Germany/Italy are eligible for omalizumab therapy. Despite proven benefits in uncontrolled severe allergic asthma, adjunctive omalizumab therapy is underutilized.

Introduction

It has been estimated that approximately 300 million people worldwide have asthma, resulting in a high burden of morbidity and mortality [1,2]. Although mild and moderate asthma can usually be controlled with inhaled corticosteroids (ICSs) and, if necessary, long-acting β_2-agonists (LABAs), many patients with severe asthma remain inadequately controlled [1,3].

The overall prevalence of asthma in Europe has been estimated to range from 5 to 18%, with approximately 20% to 30% of these patients having severe asthma [1,2]. An estimated 20% of patients with severe asthma have inadequately controlled disease [4]. In Europe, the prevalence of uncontrolled asthma among patients receiving ICSs has been estimated to range from 20 to 67% [5].

Options for patients who require additional therapy alongside an ICS and LABA include omalizumab, a humanized anti-immunoglobulin E (IgE) monoclonal antibody which is approved in the European Union (EU) as an add-on therapy for selected patients with uncontrolled severe persistent allergic asthma [6]. Omalizumab has a well-established efficacy and safety profile in patients with inadequately controlled severe allergic asthma [7—13].

Patients in Europe must fulfil a number of additional criteria to become eligible for omalizumab therapy. In particular, patients must have severe, persistent, allergic asthma with baseline IgE concentrations and bodyweights that fall within the limits set out in the approved asthma dosing tables for omalizumab. Patients must also have inadequately controlled asthma despite treatment with an ICS and LABA. Although the overall burden of asthma in Europe has been evaluated in several studies [5,14,15], epidemiological studies have not, to date, provided robust data to quantify the potential population of severe allergic asthma patients with unmet needs who could potentially benefit from omalizumab treatment.

To address this lack of information, we employed a retrospective medical record-audit approach to measure epidemiology variables based on patient-level data to assess the number of patients who could potentially benefit from omalizumab treatment ("omalizumab-eligible patients") in Italy and Germany.

Methods

To identify patients potentially eligible for omalizumab treatment we analysed retail and hospital sales data of high-dose ICS/LABA within regions of Italy and Germany. A potential candidate for omalizumab would be receiving treatment with high-dose ICS/LABA combination, therefore high-dose ICS/LABA was used as a surrogate to identify these patients.

Region selection

A region in a country consisted of a number of territorial divisions: in Germany a territorial division was a grouping of pharmacies (nanobrick) and their surrounding territories; in Italy the divisions were based on local health authorities (these definitions are national healthcare subdivisions and territorial breakdown units of the health ministry in Italy, and of the sick funds in Germany).

To identify 'extremes' of prescribing habits, the retail and hospital sales of high-dose ICS/LABA products were first deciled in each country and then the two sets of sales data (retail and hospital) were matched together by the territories in each country. Two regions were subsequently selected in Italy and Germany to represent two "extremes" of prescribing dynamics in asthma patients. For the first extreme, a region in each country was selected that fell into the top three deciles for retail sales but the bottom three deciles for hospital sales: this represented a region with high-prescribing primary care physicians (PCPs) (based on high retail and low hospital sales of ICS/LABA) indicating that a high proportion of patients (on high-dose ICS/LABA) were cared for in the primary care setting rather than under the care of a respiratory or hospital specialist: referral to a respiratory or hospital specialist was low. For the second extreme, a region in each country was selected that fell into the bottom three deciles for retail sales but the top three deciles for hospital sales: this represented a region with high-prescribing respiratory or hospital specialists (based on low retail and high hospital sales of ICS/LABA) indicating that a high proportion of patients (on high-dose ICS/LABA) were under the care of a respiratory or hospital specialist rather than in a primary care setting: referral to a respiratory specialist or hospital was high.

To illustrate that the regions chosen in each country were representative of the extreme situations, high-dose ICS/LABA sales were analysed for each country including all their territorial divisions. In Italy, one region was in the North West (Piacenza) and one region was in the centre of the country (Pescara), each with a total population of at least 250,000. High-prescribing PCP numbers were normalised per head of population; high-prescribing hospital specialist numbers were normalised per number of hospital beds. In Germany, one region combined two administrative districts in Hessen and Brandenburg (Giessen and Cottbus/Frankfurt an der Oder); the second region combined three administrative districts in Nordrhein-Westfalen (Recklinghausen/Lünen-Kamen/Hamm); each had a population of at least 850,000.

The regions were also selected according to the following criteria and with the same normalisation procedures applied as in Italy, namely per head of population in the territorial division for the office-based prescriptions

and per hospital bed in the hospital setting: 1) potential for use of high-dose ICS/LABA combinations in hospital and office-based settings; 2) sufficient population size to recruit the required number of physicians; and 3) isolation from major cities to reduce likelihood of patients migrating to hospitals in a nearby larger town.

Patient selection

Physicians in each region were then recruited if they were involved in the treatment of allergic asthma and saw at least five patients per month. Face-to-face interviews were conducted with office- and hospital-based respiratory specialists in each region as well as with PCPs and paediatricians (Germany only).

Each PCP/paediatrician had to provide information during a 1-h interview on allergic asthma patients seen by them during the previous 3 months. Patients had to be being treated with a medium- or high-dose ICS in monotherapy or in fixed combination with a LABA, to be included; approximately five patient medical records were completed per physician interview.

As respiratory specialists were more likely to see a greater number of allergic asthma patients than PCPs or paediatricians, a longer interview time was granted to allow the physician to provide a greater number of patient medical records. Included patients had persistent, moderate or severe asthma with a year-long aero-allergy, and were being treated with a medium- or high-dose ICS in monotherapy or in fixed combination with a LABA, and had been seen by the physician in the past 3 months.

The medical records completed by each participating physician were reviewed by the data collection agency (IMS Health) to ensure relevant diagnostic criteria to identify patients who were eligible for treatment with omalizumab had been correctly captured (Fig. 1).

Physicians' perceptions of a patient's asthma severity and control were captured during the interview using show cards. Levels of asthma control were defined according to the latest GINA guidelines [16]. Participating physicians were also asked to provide information on their prescribing and referral practices for each patient with a completed medical record. In Italy, it was assumed that a patient could access 11 hospitals across the two regions, therefore data on prescribing dynamics are based on the number of hospital scripts, and are not physician specific; in Germany, data are physician-specific due to fewer numbers of treating physicians across the two regions.

In order to determine the total population eligible for omalizumab in each country, the number of eligible patients per region was calculated based on the proportion of physicians interviewed vs. the total number of physicians in each region (split by speciality).

The estimated total number of omalizumab-eligible patients in each region was extrapolated based on the proportion of high-dose ICS/LABA sales in each region (by speciality) vs. the total high-dose ICS/LABA sales. The number of omalizumab-treated patients in each region was then extrapolated following the same methodology, based on total proportion of omalizumab sales in each region over the total omalizumab sales.

Results

Identification of omalizumab-eligible patients

A total of 203 face-to-face interviews were conducted with both PCPs and respiratory specialists; 95 interviews in Italy and 108 interviews in Germany. In Italy, 78 of the physicians interviewed were PCPs, seven were office-based pulmonologists and 10 were hospital-based physicians. These physicians represented 16.7% of PCPs in the selected areas, 70.0% of office-based pulmonologists and 90.9% of hospital-based physicians. In Germany, 64 of the physicians interviewed were PCPs, 17 were office-based pulmonologists, nine were paediatricians and 18 were hospital-based

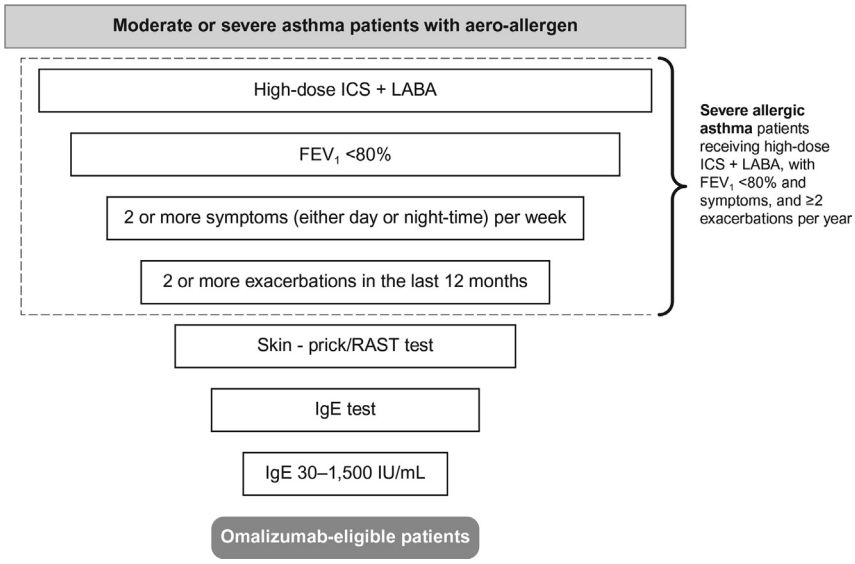

Figure 1 Screening of patient medical records for omalizumab eligibility. ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; FEV_1 = forced expiratory volume in 1 s; IgE = immunoglobulin E; RAST test = radioallergosorbent test.

physicians. These physicians represented 3.8% of PCPs in the selected areas, 5.3% of paediatricians, 53.1% of office-based pulmonologists and 30.5% of hospital-based physicians. It was estimated that the study sample represents >70% and >50% of office-based pulmonologists in the designated regions of Italy and Germany, respectively.

Medical records from 771 patients were reviewed: 235 patient medical records in Italy and 536 patient medical records in Germany. All patients had moderate or severe asthma with aero-allergen sensitivity. Overall, 115/235 (49%) patients and 147/536 (27%) patients in Italy and Germany, respectively, were receiving treatment with high-dose ICS and a LABA (Table 1).

When all screening filters are applied to the medical records, a total of 31 omalizumab-eligible patients were identified who had not previously received omalizumab: 14 (12%) in Italy and 17 (12%) in Germany (Table 1). An additional nine patients (two in Italy, seven in Germany) were currently receiving omalizumab, and five had been previously treated with omalizumab, but had discontinued.

Key reasons for non-identification of omalizumab-eligible patients

Lack of adequate testing

Overall, only 95/262 patients (36%) on high-dose ICS/LABA were documented to have received all three diagnostic tests (Table 2). In Italy, PCPs' level of testing was low, with 85% of high ICS/LABA patients not receiving tests for FEV_1, skin-prick/radioallergosorbent test (RAST) and IgE; a greater percentage of patients (69%) receiving all three tests were treated by hospital physicians. Similarly in Germany, a greater percentage of patients treated by hospital physicians received all three tests compared with patients being treated by physicians in other settings.

Table 1 Omalizumab-eligible patients identified in Italy and Germany.

	Italian patients *N* (%)	German patients *N* (%)
High-dose ICS[a] + LABA	115 (100)	147 (100)
FEV_1<80%[b]	54 (47)	96 (65)
≥2 day or night-time symptoms/week[b]	33 (29)	83 (56)
≥2 exacerbations in past year[b]	27 (23)	54 (37)
Received skin prick/RAST[b]	21 (18)	45 (31)
Received IgE test[b]	20 (17)	33 (22)
IgE 30–1500 IU/mL[b]	14 (12)	17 (12)
Total	**14 (12)**	**17 (12)**

ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; FEV_1 = forced expiratory volume in 1 s; IgE = immunoglobulin E; RAST test = radioallergosorbent test.

[a] In Italy, due to the very low proportion of patients on high-dose ICS + LABA (felt not to reflect the true proportion of patients receiving high doses) patients receiving medium and high-dose ICS + LABA were classed as 'High-dose'.

[b] Number meeting criterion for that row and all previous rows.

The majority of asthma patients on high-dose ICS/LABA in all settings are perceived to be partly or fully controlled

106/115 (92%) and 127/147 (86%) patients in Italy and Germany, respectively, who were receiving high-dose ICS/LABA treatment for severe allergic asthma were perceived by physicians as being controlled or partly controlled (Table 3). However, despite the majority of patients being perceived to be controlled or partly controlled, most patients were still experiencing exacerbations and daytime symptoms, indicating that these patients were not adequately controlled on their current therapy (Fig. 2). Furthermore, the percentage of patients in Italy experiencing exacerbations was high, regardless of whether they were perceived by physicians as being controlled, partly controlled, or uncontrolled. Some of these patients may have been eligible for omalizumab therapy, but were not receiving the treatment.

Differing prescribing and referral practices in Italy and Germany (based on physician interviews)

In Italy, omalizumab is a hospital product only; it can only be prescribed in a public hospital by a specialist physician. Omalizumab cannot be prescribed by PCPs or office-based specialists. Of the 14 patients who were eligible for treatment with omalizumab but who did not receive it, three were cared for by a PCP (although only 1 autonomously by a PCP) and three by office-based pulmonologists, one of whom refused treatment; the remaining eight patients were under the care of hospital specialists. Many patients are not considered for omalizumab because they remain in the care of PCPs and office-based pulmonologists, rather than being referred to hospital specialists. PCPs are less aware of therapy options than office-based pulmonologists; however, office-based pulmonologists are still not fully aware of the additional treatment options available to hospital specialists only. PCPs were most likely to refer patients to a specialist, with 44% and 51% stating that they would refer cases of moderate persistent and severe persistent asthma, respectively. Half of PCPs stated they would refer patients with moderate/severe asthma if they knew that specialist centres had more therapy options; only 16% of PCPs were aware of omalizumab. Office-based pulmonologists were least likely to refer patients (14% would refer patients with severe persistent asthma), while hospital-based physicians also referred relatively few patients (10% and 30% would refer patients with moderate and severe persistent asthma, respectively).

In Germany, omalizumab can be prescribed in both hospital (private and public) and office-based settings by all physicians, pending budgetary approval. Of the 17 patients who were eligible for treatment with omalizumab but who did not receive it, 11 were managed by PCPs/paediatricians, 2 by office-based pulmonologists and 4 by hospital-based physicians. The majority of omalizumab-eligible patients identified are managed by PCPs. Similarly to Italy, PCPs are less aware of therapy options than office-based pulmonologists. PCPs/paediatricians were most likely to refer patients to a specialist, with 49% stating that they would refer cases of moderate or severe persistent asthma. Office-based pulmonologists were less likely to refer patients, with 12% referring patients with moderate or severe

Table 2 Number (%) of patients documented to be tested for eligibility to receive omalizumab in Italy and Germany.

	Italy, *N* (%)				Germany, *N* (%)			
	PCPs	Office-based pulmonologists	Hospital physicians	Total in Italian regions	PCPs and paediatricians	Office-based pulmonologists	Hospital physicians	Total in German regions
No. of patients in each setting	79	10	26	115	100	26	21	147
FEV_1 tested[a]	30 (38)	5 (50)	19 (73)	54 (47)	60 (60)	16 (62)	20 (95)	96 (65)
Skinprick/RAST tested[a]	54 (68)	8 (80)	25 (96)	87 (76)	84 (84)	19 (73)	13 (62)	116 (79)
IgE tested[a]	43 (54)	8 (80)	24 (92)	75 (65)	56 (56)	16 (62)	15 (71)	87 (59)
All three tests	12 (15)	4 (40)	18 (69)	34 (30)	40 (40)	9 (34)	12 (57)	61 (41)

FEV_1 = forced expiratory volume in 1 s; IgE = immunoglobulin E; RAST test = radioallergosorbent test; PCP = primary care physician. FEV_1, skinprick/RAST, and IgE tests were not documented in all patient medical records; base used in calculations includes all patients medical records collected.

[a] Numbers reflect patients who were tested and had results that fulfilled omalizumab eligibility criteria for the particular test.

persistent asthma. Similarly, 17% of hospital-based physicians would refer patients with moderate or severe persistent asthma.

Extrapolation of results from designated regions in Italy and Germany

Analysis of the total high-dose ICS/LABA sales (including all regions in Italy and Germany) showed that the two regions chosen within the two countries were representative of the overall national situation. Further, total severe allergic asthma populations in these regions were not significantly different from the normal population distribution in these regions. To estimate the total number of omalizumab-eligible patients, data from each region (representative sample of patients treated with high-dose ICS/LABA) was extrapolated to a national level by using projection factors relating to the physician and patient populations. This extrapolation yielded >3200 and >6500 omalizumab-eligible patients in Italy and Germany, respectively. These eligible patients were in addition to those already receiving treatment with omalizumab.

Discussion

European labelling for omalizumab specifies that severe allergic asthma patients who remain uncontrolled despite treatment with ICS and a LABA must meet several specific criteria in order to be eligible for treatment; there is, however, a paucity of data describing the population of patients eligible for treatment with omalizumab in Europe. To address this current lack of information, we used a medical record-audit approach using patient-level data to characterize the number of omalizumab-eligible patients in Italy and Germany.

From a review of 771 patients' medical records in this study, 31 patients (14 patients in Italy; 17 patients in Germany) were identified who fulfilled all eligibility criteria for omalizumab treatment, but who were not currently receiving the therapy. However, there may be a number of key reasons for non-identification of omalizumab-eligible patients among this population of severe asthma patients. Firstly, approximately two-thirds of patients on high-dose ICS/LABA did not receive all three diagnostic tests (FEV_1, IgE, skin prick/RAST) to assess their eligibility for omalizumab treatment. Increasing diagnostic testing for severe

Table 3 Physician perception of patient response to current therapy in Italy (*N* = 115) and Germany (*N* = 147).

	Proportion of patients by level of asthma control (%)			
	Too soon to say	Uncontrolled	Partly controlled	Controlled
Italy				
PCPs	1	9	57	33
Office-based pulmonologists	—	0	80	20
Hospital physicians	—	4	62	35
Total in Italian regions	1	7	60	32
Germany				
PCPs and paediatricians	—	16	46	38
Office-based pulmonologists	—	8	46	46
Hospital physicians	—	10	67	24
Total in German regions		14	49	37

PCPs = primary care physicians.

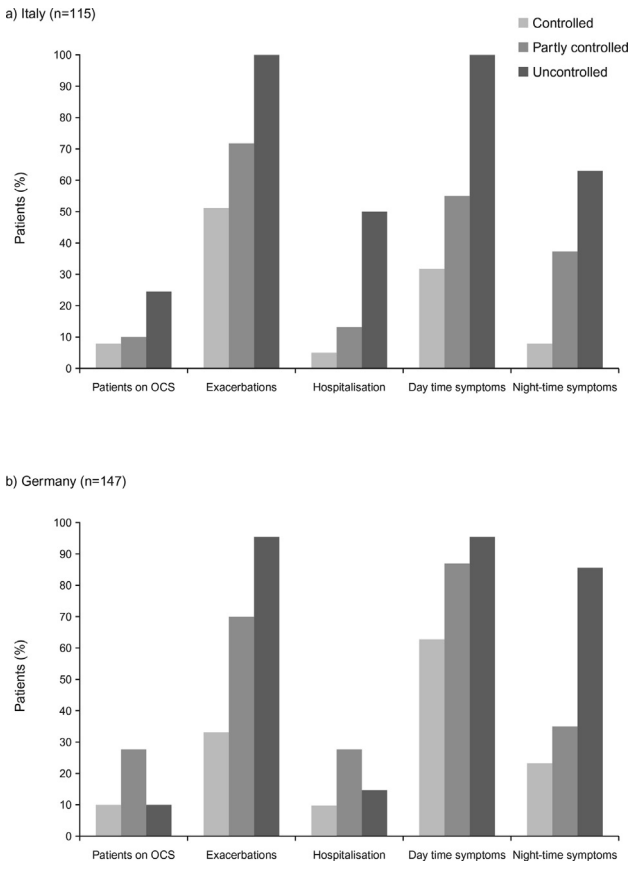

Figure 2 Level of asthma control perceived by physician and percentage of patients receiving oral corticosteroids, experiencing exacerbations, hospitalizations or symptoms.

asthmatics who remain uncontrolled on high-dose ICS/LABA may identify additional omalizumab-eligible patients who may benefit from treatment. In addition, PCPs and office-based pulmonologists often do not refer patients to hospital-based pulmonologists as they are less aware of additional treatment options available. Approximately half of the PCPs would refer patients with moderate or severe persistent asthma, and office-based pulmonologists were less likely to refer (12—14% would refer patients with moderate or severe asthma). A large number of potential omalizumab-eligible patients may therefore remain in the care of PCPs, where they are less likely to receive appropriate tests and assessments. It should also be noted that in Italy, omalizumab is a hospital product only and can only be prescribed in a public hospital by a specialist physician. Many patients are therefore not considered for omalizumab because they remain in the care of PCPs and office-based pulmonologists, rather than being referred to specialists.

Further research is required to understand the reasons why PCPs and office-based pulmonologists do not refer patients to hospital physicians, and also to raise awareness of alternative adjunctive treatments that may prove beneficial to patients with severe asthma. A high number of patients perceived by physicians to be controlled or partly controlled were still experiencing exacerbations and daytime symptoms, indicating that these patients were not adequately controlled on their current therapy. Furthermore, physicians may determine the level of asthma control in different ways, and this may not always correlate with the level of symptoms experienced by patients. There does not appear to be a comparable understanding or definition of control among physicians; control may therefore be defined differently in Italy and Germany. In this audit, the frequencies of exacerbations and hospitalizations were high, even in patients regarded by their clinicians as having controlled or partly controlled asthma.

Exacerbations and hospitalizations are indicative of poor asthma control and are associated with a risk of future exacerbations and hospitalizations [17]. Uncontrolled severe asthma patients are at a high risk of exacerbations and hospitalizations, and often have impaired quality-of-life [4]. Clinical studies of omalizumab added to current asthma therapy demonstrated that omalizumab reduced the frequency of exacerbations while improving lung function and asthma symptoms. Healthcare utilization was also reduced in these patients with uncontrolled severe allergic asthma [7—12]. Identification of omalizumab-eligible patients in Italy and Germany who remain inadequately controlled on current treatment could allow adjunctive omalizumab therapy to be initiated, which may have beneficial effects in these patients.

Omalizumab is an expensive medication, with annual acquisition costs estimated to be €11,634 to €16,766 [18,19]. In Germany and Italy, reimbursement policies have been implemented to balance economic costs with potential treatment benefits. In both countries, patients receiving omalizumab are required to be inadequately controlled on standard asthma therapies (i.e. ICS and LABAs), consistent with EU labelling [6]. Omalizumab is fully reimbursed in both Germany and Italy provided that it is used in accordance with strict criteria, generally consistent with those set out in the EU label. In addition, in Italy, omalizumab can only be prescribed by hospital-based physicians. These requirements help to ensure that omalizumab is prescribed cost effectively by restricting its use to patients with unmet needs that cannot be addressed with less expensive options. These policies may have helped to prevent the use of omalizumab when lower cost options would have been sufficient to meet patients' treatment needs. However, our results suggest that omalizumab may actually be underutilized in Germany and Italy. For patients who require additional therapy beyond ICS and LABAs, several studies have indicated that omalizumab is a cost-effective option [19—23].

Our study has a number of limitations. Firstly, the audit was based on retrospective collection of data from patient medical records. Patient selection was at the discretion of the treating physician, and indications for treatment vary between the two countries. Further, patients being treated with medium-dose ICS (and a LABA) were included within the Italy patient sample due to the low proportion of patients originally captured in Italy on high-dose ICS and LABA; this proportion was not felt to be a true reflection of the number of patients actually receiving high-dose ICS and LABA. However, exact ICS doses for patients receiving medium-dose ICS were not captured, and we have therefore assumed that ICS doses were being underestimated. Current treatment data were collected for patients seen by the treating physician in the last 3 months to allow assessment of whether the patient would be eligible for

omalizumab treatment; longer-term patient history was not collected.

In conclusion, the results of this study indicate that a significant number of patients with partly controlled/uncontrolled severe allergic asthma in Italy and Germany are eligible for omalizumab but are not receiving it. Despite proven benefits in severe allergic asthma patients, adjunctive omalizumab therapy is underutilized, partly due to inadequate referral and testing, leading to asthma remaining uncontrolled in large numbers of patients who may benefit from treatment. The extrapolation of these results to a national level estimate that over 9000 patients in Italy and Germany are potentially eligible for omalizumab treatment; these eligible patients are in addition to those already receiving treatment with omalizumab.

Conflict of interest statement

RB has served on advisory boards and is a member of speakers' bureau for AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Novartis, Roche, and Takeda. GWC has, in the last 5 years, been a scientific consultant as a single scientist or in national/international boards; a researcher in scientific trials in his university or in collaboration with other research institutions; and a speaker in scientific meetings, seminars and educational activities devoted to specialists, general practitioners and other healthcare professionals, totally or partially supported by A. Menarini, AstraZeneca, Chiesi Farmaceutici, GlaxoSmithKline, Novartis, and Takeda. DC and AGM are Novartis employees.

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